IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AFFYMETRIX, INC., a Delaware corporation, Plaintiff/Counter-Defendant, v. **ILLUMINA, INC.**, a Delaware corporation, Defendant/Counter-Plaintiff.	Civil Action No.: 04-901 JJF

ILLUMINA'S REPLY IN SUPPORT OF ITS MOTION TO VACATE AS A MATTER OF LAW THE JURY'S VERDICT OF INFRINGEMENT OF THE '716 PATENT UNDER THE DOCTRINE OF EQUIVALENTS ON THE BASIS OF PROSECUTION HISTORY ESTOPPEL

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Facing a textbook case of prosecution history estoppel on the '716 patent, Affymetrix's Opposition attempts to distract and confuse with various arguments that cannot be squared with the hard facts of the prosecution record for this patent. Affymetrix's after-the-fact advocacy cannot change the admissions that were made during prosecution of the '716 patent, or the evidence that was presented to support the doctrine of equivalents finding. The time for such calculated parsing of language was during prosecution of the patent, and by not doing it then Affymetrix must live with the consequences of its actions -- prosecution history estoppel barring application of the doctrine of equivalents on the limitation found to be met by equivalents by the jury.

Affymetrix's arguments to escape estoppel run directly contrary to the governing case law and Affymetrix's positions during prosecution and at trial. For example:

- Affymetrix now argues that the claim limitation in question was somehow not "amended," but this is contrary to its characterization in prosecution that "Applicants ***amended*** claim 60 to recite 'each probe intensity indicat[es] an extent of hybridization…'";

- Affymetrix now improperly tries to divorce the term "probe intensity" from "probe intensity indicating an extent of hybridization" to avoid the impact of its amendment, but this is contrary to Affymetrix's presentation of equivalents evidence on this limitation as a whole;

- Affymetrix now argues that the Examiner was only requesting "clarification" and "not suggesting that the scope of the claim encompassed unpatentable subject matter" (Affy. Opp. at 16), but this is directly contradicted by the fact that the claims were rejected under 35 U.S.C. § 112 ***and*** 35 U.S.C. § 103;

- Affymetrix argues that "Affymetrix certainly did not concede that it needed to amend the claim to overcome Weiss and Stockham" (Affy. Opp. at 19), but Federal Circuit case law states that a patent applicant "may not both make the amendment and then challenge its necessity in a subsequent infringement action on the allowed claim." *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1356 (Fed. Cir. 1998); and

- Affymetrix now argues the whole distinction of the '716 patent claims over Weiss and Stockham was on the basis that they did not disclose "arrays" (Affy. Opp. at 21, 24), but this ignores the fact that Affymetrix specifically argued at trial that asserted claims 1 and 5 of the '716 patent ***do not even require arrays***.

At bottom, Affymetrix spends twenty-eight pages trying to run away from the admissions it made during prosecution and at the phase one trial. But if Affymetrix wanted to argue that its amendment was unnecessary, or that the original claim language was just as broad as the amended language, it should have done so during prosecution. The Supreme Court and Federal Circuit have made very clear that the prosecution record itself must control the prosecution history estoppel analysis, and Affymetrix's belated efforts to draw fine distinctions that are found nowhere in the prosecution history must be rejected. *See, e.g., Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 344 F.3d 1359, 1369 (Fed. Cir. 2003) (noting that the prosecution history estoppel analysis must focus on "the prosecution history record, if the public notice function of a patent and its prosecution history is to have significance."). The plain facts in the record mandate that the Court find both amendment-based and argument-based estoppel, and that the jury's verdict of equivalents be vacated as a matter of law on these independent grounds.

I. THE FINDING OF EQUIVALENTS MUST BE VACATED ON THE BASIS OF AMENDMENT-BASED ESTOPPEL

The Supreme Court and Federal Circuit have laid out a relatively straightforward set of guidelines to establish amendment-based estoppel. No matter how much rhetoric Affymetrix employs in its Opposition, the facts of this case fit within these guidelines. Affymetrix originally put forth a broader claim, amended the relevant limitation in response to § 103 and § 112 rejections, and then distinguished the cited prior art by pointing to the narrower claim language. The *Festo* presumption of estoppel is triggered by Affymetrix's narrowing amendment, and Affymetrix's attempt to argue that the "tangential" exception applies is without any merit.

A. The Relevant Claim Limitation Was The Subject Of A Narrowing Amendment For A Reason Related To Patentability.

The phrase "probe intensity indicating an extent of hybridization" was added to narrow the claims in response to multiple grounds of rejection by the Examiner. As discussed below, Affymetrix's various efforts to avoid this indisputable fact are unavailing.

1. The Element On Which Equivalents Was Found Was The Subject Of A Narrowing Amendment.

Affymetrix's first argument -- that the relevant limitation was not even amended -- flies in the face of the facts and law. Affymetrix's argument boils down to arguing that the term "probe intensity" is somehow a separate and distinct limitation from the limitation "probe intensity indicating an extent of hybridization…," and thus never amended. This new-fangled parsing of the claim by Affymetrix is directly contrary to Affymetrix's own prior admissions during prosecution and at trial, well-established case law, and a common sense reading of the claim.

Contrary to Affymetrix's careful parsing of the claim language in its Opposition, Affymetrix presented proof of equivalents at the phase one trial on what it repeatedly deemed ***one claim limitation***, ***not*** a series of mini-limitations within the first clause in the body of the claim. Affymetrix treated the following clause in claim 1 of the '716 patent as a single limitation at trial:

> …computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, ***each probe intensity indicating an extent of hybridization*** of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base…

(DTX 3 at IAFP179-180 (emphasis added)). For example, when pressed prior to trial as to how it would present its doctrine of equivalents case, Affymetrix specifically stated in its response to a motion *in limine* that it would offer evidence on the following single limitation:

> Affymetrix only intends to offer doctrine of equivalents evidence … on ***the limitation*** "computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base."

(D.I. 383, Affymetrix's Response To Illumina's Motion *In Limine* #2 (emphasis added)).

Similarly, the doctrine of equivalents proof put on by Affymetrix at trial further belies Affymetrix's present effort to chop up the clause into multiple mini-limitations. The Federal Circuit requires "particularized testimony" and "linking argument" on a ***limitation-by-limitation*** basis to support a jury finding of doctrine of equivalents. *See Network Commerce, Inc. v. Microsoft Corp.*, 422 F.3d 1353, 1363 (Fed. Cir. 2005). The proof put on by Affymetrix was ***not*** particularized to the term "probe intensity" separate and apart from the rest of this limitation; to the contrary, Affymetrix's expert only supplied one substantive answer per accused product with respect to the equivalence of this entire clause of the claim. Affymetrix's expert referred to the aforementioned limitation as a whole as "this claim element" or "this middle claim element." (*See* Trial Tr. (Guerra) at 809:14-810:17, 821:17-822:19). Likewise, the argument of Affymetrix's counsel during closing also merely referred to this "middle element" without any of the parsing that Affymetrix is now engaged in. (*See* Trial Tr. (Affymetrix Closing) at 1615:23-1616:9, 1618:4-10). Affymetrix cannot be allowed to put on its "particularized" proof of equivalents on the entire "middle element" during trial and then turn around and try to chop up this limitation into a series of sub-limitations when trying to avoid its prior amendment and thus estoppel.

Indeed, several courts have ruled that such after-the-fact parsing of claim limitations is inappropriate, and cannot be used as a ploy to avoid prosecution history estoppel. *See, e.g., Cardiac Pacemakers, Inc. v. St. Jude Med., Inc.*, No. IP 96-1718-C-H/G, 2001 WL 912767, at *3 (S.D.Ind. June 14, 2001) (rejecting argument by patentee to "to parse the claim language into affected portions and unaffected portions" to avoid the impact of an amendment); *see also Lockheed Martin Corp. v. Space Systems/Loral Inc.*, 249 F.3d 1314, 1327 (Fed. Cir. 2001) (rejecting the parsing of a limitation to avoid estoppel).[1]

Even if Affymetrix did not run afoul of its own admissions before and at trial, and even if there was no case law denouncing such excessive parsing of claims, Affymetrix's argument that "probe intensity" is a completely separate limitation that was not amended during prosecution still makes no sense. The language that was added to avoid § 112 and § 103 rejections -- "indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence" -- specifically defines what the probe intensity involves.[2] The addition of claim language that modifies or defines existing claim language of course narrows the scope of the original language. *See, e.g. Ampex Corp. v. Eastman Kodak Co.*, No. Civ.A. 04-1373-KAJ, 2006 WL 3359660, at *3 (D. Del. Nov. 20, 2006) (finding the addition of "said" to modify "data" narrowed the scope of this limitation). Thus, in addition to the

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[1] Although the present standard establishes a rebuttable presumption of estoppel when a narrowing amendment is shown -- as compared to the irrebuttable presumption applied at the time in *Cardiac Pacemakers* and *Lockheed* (which was overruled by *Festo*) -- the logic behind the prohibition on parsing claim limitations to avoid an amendment and thus the presumption of estoppel applies equally under the current *Festo* standard.

[2] Moreover, if one were to read "probe intensity" separately from "indicating an extent of hybridization," and then allow the scope of equivalents to include "probe intensities" that do not indicate an extent of hybridization (like the equivalent found here), this would amount to an improper vitiation of the claim language and must be rejected. *See, e.g., Freedman Seating Co. v. Am. Seating Co.*, 420 F.3d 1350, 1358 (Fed. Cir. 2005) (the doctrine of equivalents may not be used to entirely vitiate a claim limitation).

various other legal impediments to Affymetrix's first argument, the argument simply does not comport with the language of the claim itself.

No amount of claim language gymnastics from Affymetrix can separate the limitation for which equivalents was found from the amendment of that limitation during prosecution. The predicate for the *Festo* presumption of estoppel is therefore established.

2. The Amendment Narrowed The Limitation In Question For A Reason Related To Patentability.

Affymetrix next argues that there was no "narrowing amendment" to the claims because the amendment "was added pursuant to the examiner's request to *clarify* the meaning of the claim, rather than to avoid a prior art rejection." (Affy. Opp. at 15-16 (emphasis in original)). Once again, Affymetrix's argument is inconsistent with the governing case law and the prosecution record.

Courts have routinely rejected arguments, like Affymetrix's here, that "clarifying" amendments cannot form the basis of amendment-based estoppel. *Festo* and its progeny have made very clear that amendments made to address § 112 indefiniteness rejections -- *i.e.* to "clarify" indefinite claim limitations -- ***do*** qualify as amendments that trigger a presumption of estoppel. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722, 737 (2002) ("On the other hand, if a § 112 amendment is necessary and narrows the patent's scope - even if only for the purpose of better description - estoppel may apply. A patentee who narrows a claim as a condition for obtaining a patent disavows his claim to the broader subject matter, whether the amendment was made to avoid the prior art or to comply with § 112."); *see also Ampex Corp.*, 2006 WL 3359660, at *3 (Jordan, J.) (rejecting same argument made by same counsel of record in this case, finding "contrary to Ampex's contentions, prosecution history

estoppel does indeed apply to clarifying amendments" and an "amendment is no less narrowing simply because it was made in response to a § 112.

But not only does Affymetrix's "clarification" argument fail on legal grounds, it also ignores the fact that the amendment was made in response to a prior art rejection as well. In addition to rejecting the original claims on the basis of indefiniteness under § 112, the Examiner specifically rejected all of the claims as obvious under § 103 based on Fodor in view of the Weiss or Stockham references. The amendment was therefore made, at least in part, to distinguish the cited prior art.[3] And Affymetrix's prosecution conduct after amending the claim to add the language in question further confirms that amendment was narrowing in nature. In distinguishing the Weiss and Stockham references, Affymetrix repeatedly referred to the newly-added language -- not just the original language -- to overcome the § 103 rejection. The reliance on the language added by amendment -- by both Affymetrix ***and*** then the Examiner in allowing the claims -- confirms that this amendment narrowed the claims for a reason related to patentability. *See, e.g., Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1575 (Fed. Cir. 1997) (reliance on language added by amendment to overcome a prior art rejection established estoppel).

Finally, with respect to Affymetrix's argument that the overall claim did not change in scope as a result of the amendment, this is also contradicted by review of the prosecution record. Affymetrix tries to point to language from another part of the original claim that required that

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[3] Although it does not really matter to the present analysis given *Festo*'s clarification that an amendment in response to a § 112 rejection is enough, courts have previously criticized litigants for the ploy that Affymetrix seeks to put forth here. The Federal Circuit has cautioned that "[a]n applicant may not avoid the conclusion that an amendment was made in response to prior art by discussing the amendment under the rubric of a clarification due to a § 112 indefiniteness rejection." *See Loral Fairchild Corp. v. Sony Corp.*, 181 F.3d 1313, 1326 (Fed. Cir. 1999).

probe intensities be "substantially proportional to a probe hybridizing to at least one sequence" and implies that the overall scope of the amended claim did not change.[4] Even if one attempts to follow Affymetrix's strained argument, it still falls short because a requirement that the probe intensity indicate an extent of hybridization is unquestionably narrower than language that merely requires that the intensity be substantially proportional to a probe hybridizing with a sample. Indeed, the amended language makes all the difference in the world when considering the infringement question that was presented at trial -- the claims were not literally infringed because they required that the probe intensity ***indicate the extent of hybridization*** (since Illumina's assays used enzymes to generate the intensities) -- whereas Affymetrix may have been able to prove literal infringement if the claims allowed for the probe intensity to merely require substantial proportionality to a probe hybridizing with a sequence. The change from merely requiring some relationship ("substantial proportionality") to requiring a more specific relationship ("indicating the extent of hybridization") is critical when considering that Illumina's intensities were generated from enzymatic-based assays that manipulated up-stream hybridization reactions. Thus, even if Affymetrix's "overall scope" argument is legally viable, it factually falls short as well.

Affymetrix's arguments therefore fail for a number of reasons, the relevant limitation was narrowed by amendment for patentability reasons, and the presumption of estoppel applies.

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[4] Equivalence is of course judged on a limitation-by-limitation basis, and not from the perspective of the invention as a whole. *See, e.g., Warner-Jenkinson Co. v. Hilton-Davis Chem. Co.*, 520 U.S. 17, 29 (1997).

B. Affymetrix Cannot Rebut The Presumption Of Estoppel.

Although *Festo* established three possible exceptions to rebut the presumption of estoppel, Affymetrix concedes in its Opposition that two of these three exceptions are inapplicable. Instead, Affymetrix solely relies on an argument that the amendment of the limitation in question was tangential to the adjudicated equivalent, but this requires a complete distortion of what the "tangential" exception was established to address.

The tangential exception to the *Festo* presumption of estoppel can preserve a finding of equivalence where an amendment has no real relation to the equivalent in question. *Festo Corp.*, 344 F.3d at 1368. No matter how much Affymetrix may want this exception to save the equivalents verdict, it simply has no application to the facts of this case. Affymetrix's amendment during prosecution in response to the § 112 and § 103 rejections was made at least in part to avoid prior art (including Weiss and Stockham), and then the new language in turn was used to distinguish this prior art by pointing to the newly narrowed claim limitation.

There is no dispute that the Illumina products adjudged to be equivalent use enzymes and tags to generate enhanced intensities. (*See, e.g.*, Trial Tr. (Quackenbush) at 1226:18-21, Trial Tr. (Guerra) at 873:10-13, 874:7-11). The prosecution record reveals that Weiss taught a similar approach, as described by Affymetrix itself in response to the Examiner's §103 rejection:

> …Weiss describes utilizing an ***enzyme*** on identical probes that hybridize with ***tags*** in the fragments of the nucleic acid ladder. The ***enzymes*** convert a fluorogenic substrate (e.g., BBTP) into a fluorescent product in order to ***enhance the pattern of hybridization***….

(DTX 4 at IAFP402) (emphasis added)). After noting that the prior art Weiss and Stockham references employed enzymes to generate enhanced intensities in their methods, Affymetrix stated:

> ***In stark contrast***, the present invention compares ***probe intensities that indicate the extent of hybridization*** of probes differing by a single base and the sample nucleic acid sequence.

(DTX 4 at IAFP403 (emphasis added)). The Examiner then specifically relied on the distinction that was drawn by Affymetrix, noting that "[t]he closest prior art of record is Weiss and Stockham" but that these prior art references did not teach the amended language of "…probe intensities indicat[ing] an extent of hybridization of probes differing by a single base…" (DTX 4 at IAFP414). The cold prosecution record speaks loud and clear -- the amendment was made to avoid prior art (that disclosed the use of enzymes to enhance hybridization intensities) and was central to the allowance of the claims.

This is the antithesis of a tangential amendment. "[A]n amendment made to avoid prior art that contains the equivalent in question is ***not*** tangential; it is central to allowance of the claim."[5] *Festo Corp.*, 344 F.3d at 1369 (emphasis added). It is indisputable that (1) Affymetrix made its amendment (at least in part) to avoid the Weiss and Stockham prior art[6], and (2) Weiss and Stockham contain the equivalent in question (intensities enhanced by the use of enzymes). There is no need to go further in the analysis -- the amendment cannot possibly qualify as tangential. The pages upon pages that Affymetrix spends distorting and distinguishing the Weiss

[5] Affymetrix states "that the prosecution history contains no indication that the claim was amended to overcome the prior art." (Affy. Opp. at 21 n.3) Affymetrix's statements are simply incorrect as issued claims 1 and 5 of the '716 patent contain the same amended language first present in amended claim 60, which was amended to overcome a § 103 prior art rejection. (DTX 4 at IAFP390, 399, 402-403). *See Ampex Corp. v. Eastman Kodak Co.*, 460 F.Supp.2d 563, 568 (D.Del. 2006) ("Any subject matter surrendered via claim amendments during prosecution is also relinquished for other claims containing the same limitation.") (quoting *Glaxo Wellcome, Inc. v. Impax Labs., Inc.*, 356 F.3d 1348, 1356 (Fed. Cir. 2004).

[6] As mentioned above, a patent applicant cannot amend claims in the face of a prior art rejection and then argue later that the amendment was not needed to avoid the prior art. *See, e.g., Bai*, 160 F.3d at 1356.

and Stockham prior art references have no bearing on the presumption of estoppel or Affymetrix's inability to rebut it.[7]

Even if Affymetrix's new arguments to distinguish Weiss and Stockham are considered, however, they are inconsistent with the prosecution record and Affymetrix's own prior statements in this case. Affymetrix now argues that the entire focus of the prosecution arguments was to distinguish the "sequencing ladders"[8] of Weiss and Stockham from the "arrays" of the '716 patent. (Affy. Opp. at 21, 24). Affymetrix cannot cite, however, to a single statement in the prosecution record that draws a distinction on the basis of this "arrays" argument. Indeed, there is no such evidence in the prosecution record. And this is not surprising, as Affymetrix itself when arguing about the scope of the claims in this case has specifically noted that asserted claims 1 and 5 of the '716 patent ***do not even require the use of arrays.*** (*See, e.g.*, Markman Hearing Tr. at 60 (when describing claims 1 and 5 of the '716 patent, Affymetrix's counsel argued "the probes don't need to be an array"); Trial Tr. (Affymetrix Closing) at 1622:9-12 ("What that shows that you don't always have to be in an array of probes. The other claims [*i.e.* 1 and 5] cover where there aren't [an] array of probes.")). Thus, Affymetrix's new argument that the claims were distinguished on the basis that they

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[7] Affymetrix's arguments to identify differences between Weiss and Stockham and the '716 patent claims are misguided because, *inter alia*, they completely ignore the fact that Weiss and Stockham were cited as ***part of*** § 103 obviousness ***combinations***. To the extent that Affymetrix is even correct about some of the distinctions it attempts to draw with the Weiss and Stockham references -- and many are in fact gross distortions -- the reality is that these trivial differences are in fact taught by the Fodor reference that was cited in combination with Weiss and Stockham, so they are really irrelevant to the patentability of the claims as discussed during prosecution.

[8] Affymetrix's use of the term "sequencing ladders" to describe the prior art cannot obscure the fact that these references disclose enzymatic-enhanced intensities from hybridization reactions, and these intensities are then used to make base calls (*i.e.* determine sequence), very similar to the enzymatic-based assays used in Illumina's products.

required the use of "arrays" is completely inconsistent with their prior arguments that these claims do not even require arrays.

The cases Affymetrix cites also are of no moment. For example, Affymetrix's reliance on *Insituform Technologies, Inc.* presupposes that there is no relationship between the narrowing amendment and the alleged equivalent -- this is simply not the case here. *See, e.g., Insituform Techs., Inc. v. CAT Contracting, Inc.*, 385 F.3d 1360, 1370 (Fed. Cir. 2004) ("There is no indication in the prosecution history of any relationship between the narrowing amendment and a multiple cup process, which is the alleged equivalent in this case.") Where Affymetrix specifically noted that the prior art disclosed enzymatic-generated intensities, and at the same time amended its claims and expressly argued with respect to patentability due to the limitation directly tying probe intensities to the "extent of hybridization" (as opposed to the extent of enzymatic reaction or something else), Affymetrix's rationale underlying the amendment is anything but tangential.[9] *Biagro W. Sales, Inc. v. Grow More, Inc.*, 423 F.3d 1296, 1306 (Fed. Cir. 2005) (holding patentee "***cannot*** claim that the rationale for the amendment is merely tangential" when the reason for the amendment and the accused equivalent in the case both relate to the concentration of the fertilizer) (emphasis added).

Affymetrix's amendment of the claim limitation in question was anything but tangential to the adjudged equivalent, and thus Affymetrix cannot overcome the presumption of estoppel. The finding of infringement under the doctrine of equivalents must be vacated on the basis of amendment-based prosecution history estoppel.

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[9] In what may be its most desperate argument, Affymetrix states that it "no more distinguished the use of 'enzymes' or 'tags' than it did 'DNA.'" (Affy. Opp. at 22). The difference, of course, is that Affymetrix did expressly distinguish the prior art on the basis that they employed enzymes and tags, but never mentioned DNA as a point of distinction (because it is not).

II. THE FINDING OF EQUIVALENTS MUST ALSO BE VACATED ON THE BASIS OF ARGUMENT-BASED ESTOPPEL

In addition to establishing amendment-based estoppel, Affymetrix's arguments during prosecution also form the basis to find argument-based estoppel as well. The analysis of argument-based estoppel has a somewhat different focus than amendment-based estoppel; because there is no presumption of surrender based on a narrowing amendment, the analysis centers on what was "clearly and unmistakably" surrendered by the statements made during prosecution. *Deering Precision Instruments, L.L.C. v. Vector Distrib. Sys., Inc.*, 347 F.3d 1314, 1326 (Fed. Cir. 2003). Thus, while many of Affymetrix's arguments regarding the prior art and what was specifically said during prosecution are largely irrelevant to the amendment-based estoppel analysis, these arguments are at least potentially germane to the argument-based estoppel analysis. In any event, the prosecution record still reveals that Affymetrix clearly and unmistakably surrendered the enzymatic-type assays that were found equivalent by the phase one jury, and a finding of argument-based estoppel is thus warranted as well.

Affymetrix surrendered the alleged equivalent -- use of enzymes and/or tags for labeling and detection -- through its distinction of the Weiss and Stockham prior art references during prosecution. Affymetrix specifically called out the presence of enzymes and tags in these prior art references, and specifically noted the impact of enzymes on the intensities from hybridization reactions. Affymetrix was then very clear in drawing the distinction between the enzymatic-enhanced intensities of the prior art and the intensities generated by the invention of the '716 patent, stating that "***[i]n stark contrast***, the present invention compares probe intensities that indicate the extent of hybridization of probes differing by a single base and the sample nucleic acid sequence." (DTX 4 at IAFP403) (emphasis added). While Affymetrix now tries to distract attention to the arguments in prosecution relating to fluorescent signals and other differences in

the prior art, these arguments merely flow from the fact that the prior art used enzymatic-based assays and the '716 patent claims did not.

The cases cited by Affymetrix do not undermine a finding of argument-based estoppel. Affymetrix fails to point out that in *AquaTex* "[t]here [was]…no indication in the prosecution history whether or not AquaTex agreed or disagreed with the examiner's statement that the fiberfill found in the prior art comprised natural fibers." *AquaTex Indus., Inc. v. Techniche Solutions*, 419 F.3d 1374, 1383 (Fed. Cir. 2005). In this case, however, Affymetrix squarely addressed the § 103 rejection by the Examiner, and in conjunction with its amendment clearly and unmistakably called out the alleged equivalent while distinguishing the claim limitation from Weiss and Stockham. (Ill. Br. at 17-18; DTX 4 at IAFP402-403) More particularly, Affymetrix expressly noted the use of enzymes, and their impact on the signal or intensity, in drawing distinctions over the prior art. Although Affymetrix may have described other aspects of the Weiss and Stockham references as well, these "other distinctions" do not avoid the fact that use of enzymes to enhance intensities was relinquished. *See, e.g.*, *Southwall Tech., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1582-83 (Fed. Cir. 1995) (criticizing the interpretation of *Read Corp. v. Portec, Inc.*, 970 F.2d 816 (Fed. Cir. 1992) put forth by Affymetrix here (*see* Affy. Opp. at 25), explaining that "*Read* does not hold … that arguments made during prosecution can *only* create an estoppel regarding the combined distinctions and can never create separate estoppels…. For instance, any argument made regarding the need to distinguish the prior art … does create a separate estoppel, regardless of other distinctions made.").

Affymetrix cannot be allowed to distinguish Weiss and Stockham during prosecution on the basis of their use of enzymes and/or tags, and then switch course and argue that they only distinguished certain uses of enzymes and tags when trying to evade a finding of estoppel.

Contrary to the picture that Affymetrix seeks to paint in its brief, the enzymes in the Weiss and Stockham references perform the same basic function as those used in the Illumina products adjudged to infringe -- enhancing (*i.e.* sharpening) the intensity from a hybridization reaction. In any event, Affymetrix certainly did not compare and contrast different forms of enzymes or tags when distinguishing the prior art during prosecution. Affymetrix cannot introduce a new extra-fine level of distinction for the first time in its briefing on prosecution history estoppel; Affymetrix's more general arguments during prosecution must govern the analysis. *See, e.g.*, *Lockwood*, 107 F.3d at 1575 (rejecting patentee's attempt to avoid estoppel by drawing a finer distinction between alpha-numeric displays and graphical displays where such a distinction was not drawn during prosecution).

Since Illumina's products that were found to infringe under the doctrine of equivalents employ the use of enzymes and/or tags for labeling and detection, the principles of argument-based estoppel also dictate that the finding of equivalents be vacated.

CONCLUSION

For the foregoing reasons, Illumina respectfully requests that this Court grant its Motion to Vacate the Jury's Verdict of Infringement of the '716 Patent as a Matter of Law and find that Affymetrix is estopped from asserting the Doctrine of Equivalents.

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EXCERPTS FROM

DTX 3

US005795716A

United States Patent [19]

Chee et al.

[11] Patent Number: 5,795,716

[45] Date of Patent: Aug. 18, 1998

[54] COMPUTER-AIDED VISUALIZATION AND ANALYSIS SYSTEM FOR SEQUENCE EVALUATION

[76] Inventors: Mark S. Chee, 3199 Waverly St., Palo Alto, Calif. 94306; Robert J. Lipshutz, 970 Palo Alto Ave., Palo Alto, Calif. 94381

[21] Appl. No.: 327,525

[22] Filed: Oct. 21, 1994

[51] Int. Cl.[6] C12Q 1/68; C12P 19/34; G06F 15/46; C07H 21/04

[52] U.S. Cl. 435/6; 435/91.1; 435/91.2; 382/178; 382/179; 364/96; 364/97; 364/98; 364/99; 536/24.3; 536/24.33; 536/24.32; 536/23.1

[58] Field of Search 382/178, 179; 435/5, 6, 91.2, 91.1, 7.1, 7.2, 23.1; 536/24.3, 24.33, 96, 97, 98, 99

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Primary Examiner—W. Gary Jones
Assistant Examiner—Dianne Rees

[57] ABSTRACT

A computer system for analyzing nucleic acid sequences is provided. The computer system is used to perform multiple methods for determining unknown bases by analyzing the fluorescence intensities of hybridized nucleic acid probes. The results of individual experiments are improved by processing nucleic acid sequences together. Comparative analysis of multiple experiments is also provided by displaying reference sequences in one area and sample sequences in another area on a display device.

10 Claims, 26 Drawing Sheets

Microfiche Appendix Included
(5 Microfiche, 272 Pages)

-continued

(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (oligonucleotide)

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:35:

ACAOOGXROO A 11

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (oligonucleotide)

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:36:

CTOOOOOGTA T 11

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (oligonucleotide)

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:37:

CTGOCCSGTO T 11

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (oligonucleotide)

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:38:

CTOOOCOGTA T 11

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(i i) MOLECULE TYPE: DNA (oligonucleotide)

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:39:

CTOOCACGTO T 11

What is claimed is:

1. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:

computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of said plurality of probe intensities to each other;

computer code that generates a base call identifying said unknown base according to results of said comparison and said sequences of said nucleic acid probes; and

a computer readable medium that stores said computer codes.

A computer program product that identifies an ɔown base in a sample nucleic acid sequence, compris-

ɔmputer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

ɔomputer code that calculates a ratio of a higher probe intensity to a lower probe intensity;

ɔomputer code that generates a base call identifying said unknown base according to a base of a nucleic acid probe having said higher probe intensity if said ratio is greater than a predetermined ratio value; and

a computer readable medium that stores said computer codes.

3. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:

computer code that receives a first set of signals corresponding to a first set of probe intensities, each probe intensity in said first set indicating an extent of hybridization of a nucleic acid probe with a reference nucleic acid sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that receives a second set of signals corresponding to a second set of probe intensities, each probe intensity in said second set indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of at least one of said probe intensities in said first set and at least one of said probe intensities in said second set;

computer code that generates a base call identifying said unknown base according to results of said comparisons said sequence of said nucleic acid probe; and

a computer readable medium that stores said computer codes.

4. A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:

computer code that receives signals corresponding to statistics about a plurality of experiments, each of said experiments producing probe intensities, each probe intensity indicating an extent of hybridization of a nucleic acid probe with a reference nucleic acid sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that receives a plurality of signals corresponding to probe intensities, each probe intensity indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of at least one of said plurality of probe intensities with said statistics;

computer code that generates a base call identifying said unknown base according to results of said comparison and said sequence of said nucleic acid probe; and

a computer readable medium that stores said computer codes.

5. A system that identifies an unknown base in a sample nucleic acid sequence, comprising:

a processor; and

a computer readable medium coupled to said processor for storing a computer program comprising:

computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of said plurality of probe intensities to each other; and

computer code that generates a base call identifying said unknown base according to results of said comparison and said sequences of said nucleic acid probes.

6. A system that identifies an unknown base in a sample nucleic acid sequence, comprising:

a processor; and

a computer readable medium coupled to said processor for storing a computer program comprising:

computer code that receives a plurality of signals corresponding to probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that calculates a ratio of a higher probe intensity to a lower probe intensity; and

computer code that generates a base call identifying said unknown base according to a base of a nucleic acid probe having said higher probe intensity if said ratio is greater than a predetermined ratio value.

7. A system that identifies an unknown base in a sample nucleic acid sequence, comprising:

a processor; and

a computer readable medium coupled to said processor for storing a computer program comprising:

computer code that receives a first set of signals corresponding to probe intensities, each probe intensity in said first set indicating an extent of hybridization of a nucleic acid probe with a reference nucleic acid sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that receives a second set of signals corresponding to probe intensities, each probe intensity in said second set indicating an extent of hybridization of a nucleic acid probe with said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

computer code that performs a comparison of at least one of said probe intensities in said first set and at least one of said probe intensities in said second set; and

computer code that generates a base call identifying said unknown base according to results of said comparison and said sequence of nucleic acid probe.

8. A system that identifies an unknown base in a sample nucleic acid sequence, comprising:

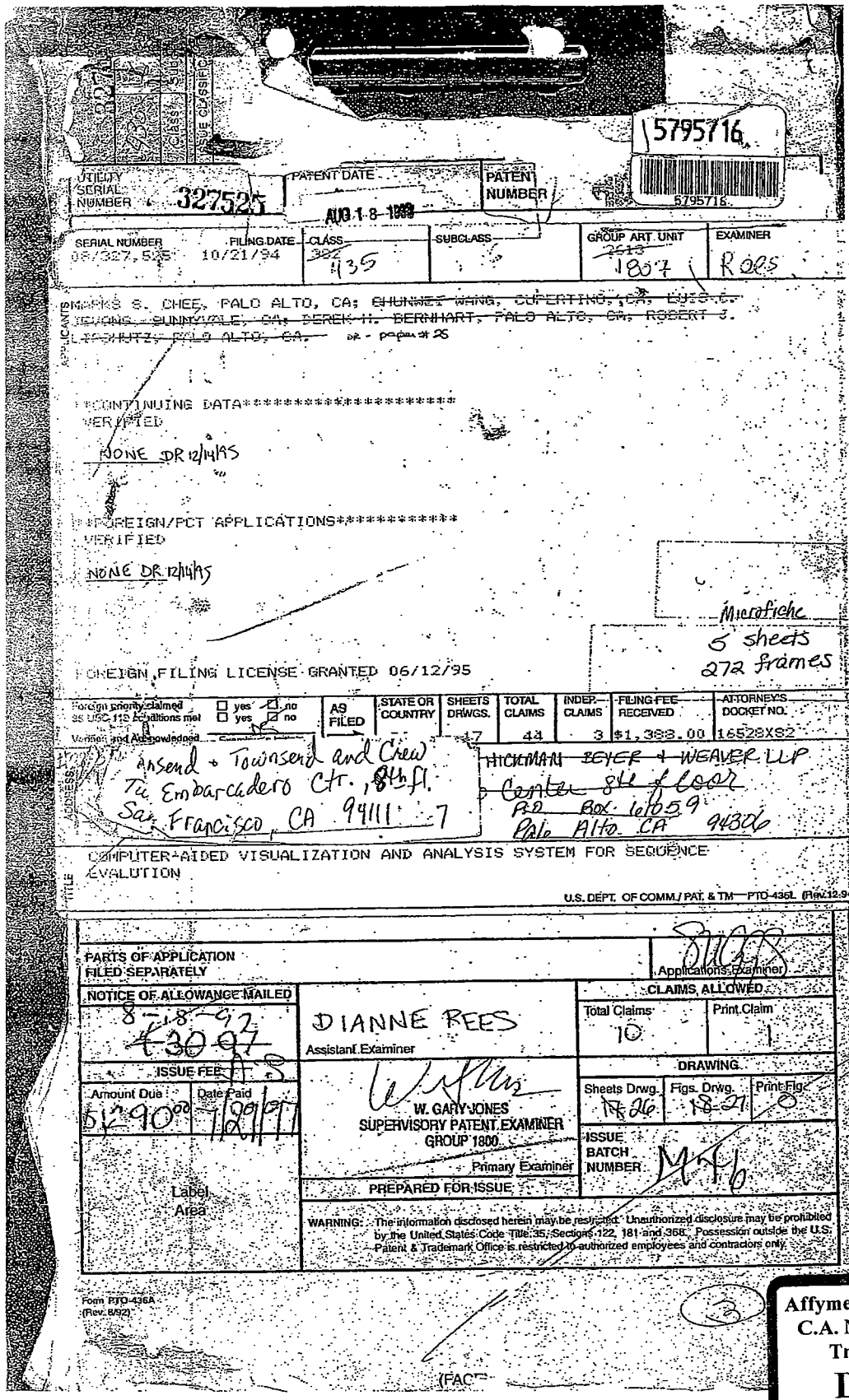
a processor; and

a computer readable medium coupled to said processor for storing a computer program comprising:

computer code that receives signals corresponding to statistics about a plurality of experiments, each of said experiments producing probe intensities, each probe intensity indicating an extent of hybridization of a nucleic acid probe with a reference nucleic acid

EXCERPTS FROM

DTX 4



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UTILITY SERIAL NUMBER 327525 | PATENT DATE AUG 18 1998 | PATENT NUMBER 5795716

SERIAL NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
08/327,525	10/21/94	382 435		1807	Rees

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CONTINUING DATA*******
VERIFIED
NONE DR 12/14/95

FOREIGN/PCT APPLICATIONS********
VERIFIED
NONE DR 12/14/95

Microfiche
5 sheets
272 frames

FOREIGN FILING LICENSE GRANTED 06/12/95

Foreign priority claimed 35 USC 119 conditions met Verified and Acknowledged	AS FILED	STATE OR COUNTRY	SHEETS DRWGS.	TOTAL CLAIMS	INDEP. CLAIMS	FILING FEE RECEIVED	ATTORNEY'S DOCKET NO.
☐ yes ☑ no ☐ yes ☑ no			17	44	3	$1,388.00	16528XS2

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TITLE: COMPUTER-AIDED VISUALIZATION AND ANALYSIS SYSTEM FOR SEQUENCE EVALUATION

U.S. DEPT. OF COMM./ PAT. & TM — PTO-436L (Rev.12-9

PARTS OF APPLICATION FILED SEPARATELY

Applications Examiner

NOTICE OF ALLOWANCE MAILED
8-18-97

DIANNE REES
Assistant Examiner

CLAIMS ALLOWED
Total Claims: 10 | Print Claim: 1

ISSUE FEE
Amount Due: $1190.00 | Date Paid: 12/01/97

W. GARY JONES
SUPERVISORY PATENT EXAMINER
GROUP 1800
Primary Examiner

DRAWING
Sheets Drwg.: 17 26 | Figs. Drwg.: 18-21 | Print Fig.: 8

ISSUE BATCH NUMBER: M46

PREPARED FOR ISSUE

Label Area

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Form PTO-436A (Rev. 8/92)

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Affymetrix v. Illumina
C.A. No 04-901 JFF
Trial Exhibit
DTX 4

IAFP00000182

I hereby certify that this correspondence is being sent by facsimile transmission to: Examiner D. Rees, Ph.D. Fax No.: 1-703-305-7401 Assistant Commissioner for Patents, Washington, D.C. 20231, on May 20, 1996

By Christina A. Bybee
Christina A. Bybee

PATENT

Attorney Docket No. 16528X-008200
(client file no. 1091)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
MARK S. CHEE ET AL.

Application No.: 08/327,525

Filed: October 21, 1994

For: COMPUTER-AIDED VISUALIZATION AND ANALYSIS SYSTEM FOR SEQUENCE EVALUATION

Examiner: D. Rees

Art Unit: 1807

AMENDMENT

RECEIVED
MAY 20 1996
GROUP 1800

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action mailed December 19, 1995, for which a petition for an extension of time is enclosed, please amend this application as follows.

IN THE CLAIMS:

Please cancel claims ~~1, 3-20~~ and ~~45-59~~ without prejudice. Please add new claims 60-105 as follows.

1-59. --CANCELED--

60. In a computer system, a method of identifying an unknown base in a sample nucleic acid sequence, said method comprising the steps of:

inputting a plurality of probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by a single base;

a) In regard to claim 1, the Examiner stated that it is not clear how a probe intensity is associated with a nucleic acid probe. As the Examiner suggested, Applicants amended claim 60 to recite "each probe intensity indicat[es] an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence." Accordingly, the rejection does not apply to the new claims.

b,c) Also in regard to claim 1, the Examiner stated that "substantially" and "associated" were indefinite or lack antecedent basis. As claim 60 does not contain these words, the rejection does not apply to the new claims.

d) In regard to claim 1, the Examiner stated that it is unclear how "calling" is defined. Claim 60 recites instead "identifying said unknown base" as was suggested by the Examiner in paragraph e). The Examiner also stated that there seems to a step missing. Applicants do not believe that any steps are missing in claim 60. Accordingly, the rejection does not apply to the new claims.

e) In regard to claim 4, the Examiner stated that the phrase "calling said unknown base as being a base" is unclear. Claim 60 recites instead "identifying said unknown base" as suggested by the Examiner. Additionally, the Examiner stated that it is unclear what a "predetermined ratio value" is. A predetermined ratio value is typically a constant number like 1.2 (see, e.g., claim 63). In the interview, it is believed that the Examiner tentatively agreed that this phrase is patentably definite.

f) In regard to claim 6, the Examiner stated that the "step of sorting" is unclear. Claim 64 recites that a step of sorting probe intensities is done "before said comparing step" (see, e.g., page 14, lines 17-22). Accordingly, the rejection does not apply to the new claims.

g) In regard to claim 9, the Examiner stated that it is unclear how "wild-type" is defined with respect to the "reference sequence." Claim 67 recites that the wild-type probe intensity indicates the extent of hybridization of a complementary probe with the reference sequence. Since the reference sequence is a

(identifying) methods of the present invention. For the following reasons, these references do not disclose or suggest the present invention as claimed.

Weiss and Stockham are related to nucleic acid sequencing which utilizes nucleic acid ladders which may be formed by well known techniques such as the Sanger dideoxy method or the Maxam and Gilbert method. More specifically, Weiss describes utilizing an enzyme on identical probes that hybridize with tags in the fragments of the nucleic acid ladder. The enzymes convert a fluorogenic substrate (e.g., BBTP) into a fluorescent product in order to enhance the pattern of hybridization (see, e.g., Fig. 1C).

Stockham, more specifically, describes methods of sharpening signal peaks from electrophoretic migration patterns of nucleic acid ladders. Each fragment of the nucleic acid ladder is labeled with a radioactive label which is utilized to identify the position of the fragment on the gel following electrophoresis. As analyzing the migration patterns is time consuming and often error prone, Stockham describes equations and formulas for increasing the accuracy of this process (e.g., sharpening signal peaks).

Weiss and Stockham do not disclose or suggest inputting probe intensities to identify an unknown base where the probe intensities indicate the extent of hybridization of probes differing by a single base and the sample nucleic acid sequence. Claim 60 recites the following:

> inputting a plurality of probe intensities for a plurality of nucleic acid probes, each probe intensity indicating an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by a single base;

(emphasis supplied). Neither Weiss nor Stockham discloses these limitations.

Initially, Weiss uses a single probe which will hybridize to a tag on the nucleic acid ladder fragments. As such, all of the "probes" in Weiss are identical. Furthermore, the probes in Weiss do not indicate the extent of hybridization but instead are utilized to generate a fluorescent signal which

indicates the location of a fragment on the substrate. Accordingly, it is the location of the fragments that is utilized to sequence a nucleic acid.

Stockham does not utilize probes at all. Instead, Stockham recites that the fragments of the nucleic acid ladder are radioactively labeled. The radioactive signal resulting indicates the position of the fragments on the gel in a way which is similar to Weiss. Accordingly, Stockham also utilizes the location of the fragments to sequence a nucleic acid.

In stark contrast, the present invention compares probe intensities that indicate the extent of hybridization of probes differing by a single base and the sample nucleic acid sequence. Claim 60 recites the following:

> said computer system comparing said plurality of probe intensities; and
> identifying said unknown base according to results of said comparing step.

In the Office Action, the Examiner stated that it would have been prima facie obvious to one of ordinary skill in the art to use the computer algorithms of Weiss and Stockham to interpret that data from the sequencing by hybridization described by Fodor. More specifically, the Examiner stated that one could "call" a site based on the intensity of a signal produced by a probe at that site and thus assign an identity to that site. Applicants disagree.

Weiss and Stockham relate to vastly different technologies than the pioneering advances of Fodor. Weiss and Stockham are directed to identifying the location of a fragment of a nucleic acid ladder. In the present invention, the locations of the hybridized probes are known and, as such, the computer algorithms of Weiss and Stockham would indeed seem to teach away from the present invention which is directed to calling an unknown base according to probe intensities from nucleic acid probes that differ by a single base.

As Weiss and Stockham do not disclose or suggest all the limitations of claim 60, the claim is patentably distinct over the references. All the other pending claims contain similar limitations. Therefore, Applicants request that all the

Claims 60-105 are allowable over the prior art of record. The closest prior art of record is Weiss and Stockham who teach equations and formulas for sharpening signal peaks derived from electrophoretic migration patterns of nucleic acid ladders. Weiss and Stockham do not teach or fairly suggest a method if inputting probe intensities to identify an unknown base where the probe intensities indicate the extent of hybridization of probes differing by a single base and the same nucleic acid as recited in the base claim, claim 60.

No claims are allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 305-7401. Please note that the faxing of such papers must conform with the notice to Comply published in the Official Gazette, 1096 OG 30 (Nov 15, 1989).

An inquiry regarding this communication should be directed to examiner Dianne Rees, Ph.D., whose telephone number is (703) 308-6565. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1156.

Calls of a general nature may be directed to the Group receptionist who may be reached at (703) 308-0196.

Dianne Rees
Dianne Rees

July 8, 1996

W. GARY JONES
SUPERVISORY PATENT EXAMINER
GROUP 1800
7/8/96